Pathogenesis of Poliomyelitis*†

DAVID BODIAN, M.D.

Poliomyelitis Laboratory, Department of Epidemiology, Johns Hopkins University, Baltimore, Md.

SOME recent observations have suggested that it is time to review the evidence on the pathogenesis of poliomyelitis with a fresh point of view and especially to reëxamine the rapidly weakening concept of poliomyelitis as a disease in which virus only invades and multiplies in nervous tissue. First of all, the work of Enders' group [1] in growing poliomyelitis virus in tissue culture has made it less difficult to accept the possibility that virus may multiply in non-nervous tissues. Second, the recent finding by several workers that antibody is already present in the serum of individuals at the time of onset of paralysis [2-4] has led to a discounting of the many unsuccessful attempts to find virus in the blood of paralytic human cases,[5] and has reopened the question of the occurrence of a viremia in the preparalytic period, such as occurs in other neurotropic virus diseases. In fact, the two reported isolations of virus from the blood of patients [5, 6] appear in the light of a rapid antibody response to support rather than to discount the possibility that viremia may be a regular occurrence early in the disease, especially since in one instance the virus was isolated not more than six hours after onset of an abortive illness.[5] The isolation of virus in the blood stream of cynomolgus monkeys and of chimpanzees in the incubation period after simple virus feeding by Dr. D. M. Horstmann at Yale [7] and by us,[8] also has suggested that a viremia occurs early in the human disease. Such an occurrence would raise the important question of whether the viremia is merely an incidental phase of the disease or whether it is related to the occurrence of paralysis or the development of antibody.

As a point of departure in the analysis of this problem, I should like to discuss our findings in chimpanzees. By every criterion which can now be applied, the disease which follows simple virus feeding in chimpanzees is similar to that which occurs in human beings. A high rate of alimentary infection, and low rate of paralytic disease, are common to both species, and clinical and pathological aspects of the infection are indistinguishable.[9, 10] Serum antibody formation in chimpanzees appears to be similar in time course and in magnitude to that which occurs in human beings given virus by mouth, as reported by Koprowski.[11] Finally, natural paralytic and silent infections may occur in chimpanzees, since not only were two cases described in a children's zoo in Cologne,[12] but also instances of accidental infection have occurred in two laboratories.[13, 14]

The chimpanzees first to be described were inoculated by means of simple virus feeding and subsequently were studied in detail in regard to time of occurrence of fecal virus excretion, viremia, paralysis, and serum antibody formation. The virus used, the Wallingford strain, is infective in rodents

* Don W. Gudakunst Memorial Lecture presented at the School of Public Health, University of Michigan, Ann Arbor, Mich., May 13, 1952.

† The work reported in this paper was aided by a grant from the National Foundation for Infantile Paralysis, Inc. The lecture was based in part on material published in greater detail in references 8 and 39.

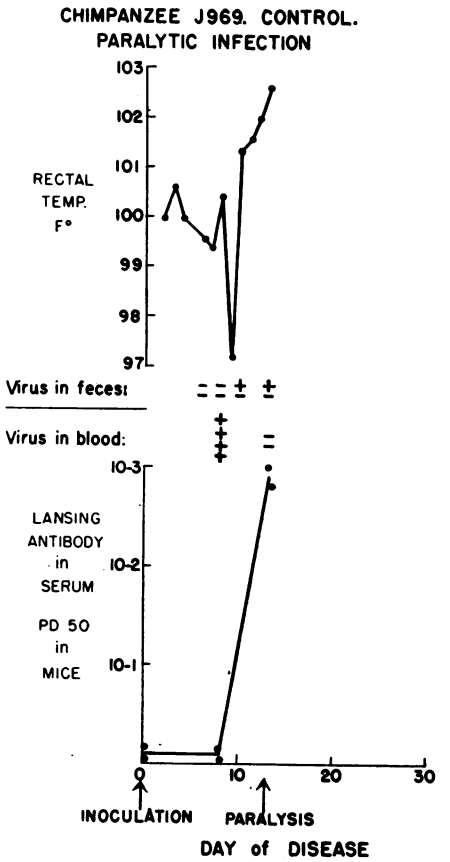

FIGURE 1—Paralytic poliomyelitis infection in chimpanzee J-969 after single feeding of 5 ml. of 20 per cent suspension of rhesus spinal cord containing 1,000 intracerebral PD_{50}s of Wallingford strain (Type 2) per ml. + = paralytic poliomyelitis in rhesus monkey inoculated with chimpanzee fecal suspension (intranasally), or undiluted serum (intracerebrally). — = absence of infection in rhesus monkey similarly inoculated. Positive and negative results confirmed by histological examination of spinal cord sections after 30 days. Note viremia on eighth day, when virus titer in serum was $10^{-1.5}$.

and is of the Lansing type (Type 2), so that specific antibody formation could be studied in quantitative detail by means of mouse neutralization tests, with 32 PD_{50} of virus, and tenfold serum dilutions.

Of 4 young chimpanzees which had no previous specific antibody in their sera, 2 were paralyzed after incubation periods of 13 and 17 days respectively (Figures 1 and 2). In both animals the only clinical sign which preceded the sudden onset of paralysis was fever. Two striking findings are, first, the demonstration of viremia preceding the onset of paralysis by 5 and 2 days respectively, and the sharp rise of antibody immediately thereafter. The occurrence of specific antibody at the time of paralysis has been observed in human cases and may account for the usual failure to isolate virus from the blood of patients, or of paralyzed animals infected by virus feeding. A third chimpanzee was shown to have a viremia on the eighth and eleventh days after virus feeding and a sharp rise of antibody immediately thereafter, but no

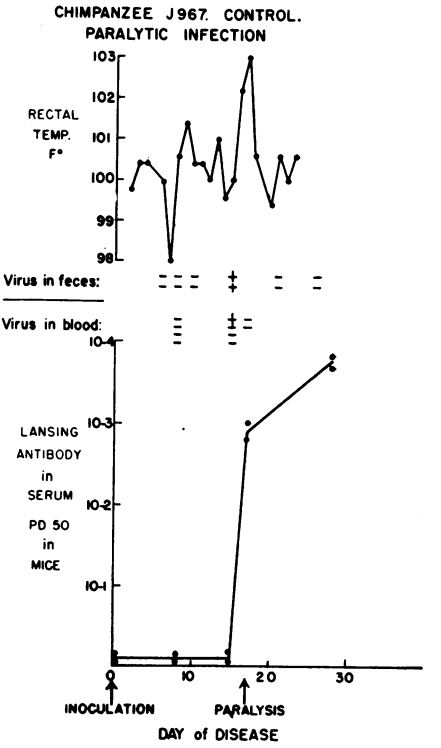

FIGURE 2—Paralytic poliomyelitis infection in chimpanzee J-967 after virus feeding similar to that in animal J-969. Symbols as in Figure 1. Note rise of serum antibody from 0 to titer of 10^{-3} in a period of 2 days.

signs of infection were noted until pathological examination 2 months later revealed he had experienced a typical nonparalytic infection of the CNS. In the fourth chimpanzee, virus was not isolated from the blood on the eighth day after virus feeding, preceding the appearance of serum antibody. It is interesting that this chimpanzee showed no signs of poliomyelitis, but experienced an alimentary infection, and showed a slower antibody rise than occurred in the 2 paralytic cases. These results will now be discussed in relation to other evidence bearing on the principal problems of pathogenesis in primate poliomyelitis.

In regard to the portals of entry and of exit, at the present time there appears to be almost complete agreement that the virus of poliomyelitis usually is spread by person-to-person contact, and that it probably enters the body via the mouth. There is also general agreement that exit occurs by way of alimentary secretions or excretions, although it is not clear whether oropharyngeal secretion or fecal material is the principal vehicle of spread of infection. There has been much less agreement, and no critical evidence, however, regarding the way in which the virus penetrates from the periphery to reach the central nervous system. This, in fact, has been one of the most elusive problems in the pathogenesis of poliomyelitis.

Soon after the opening of the era of experimental transmission of the disease to monkeys, the successful infection of monkeys by intranasal inoculation appeared to establish the olfactory system as the principal pathway for virus penetration to the central nervous system. This concept was strengthened by the later demonstration of a progressive spread of virus and of lesions from olfactory mucosa, to olfactory bulbs, and down the brain stem to the spinal cord. After a period of over two decades, this concept of an olfactory pathway for virus spread to the CNS finally was overwhelmed by contrary evidence. Studies on virus and lesion distribution in many fatal human cases demonstrated conclusively that neither virus nor characteristic histopathological changes could be found in the olfactory system, although the distribution of these signs of infection in the rest of the nervous system was remarkably similar in human cases and in experimentally infected primates.[15-20] This finding concentrated attention in this country on observations from abroad,[21] soon abundantly confirmed, that virus could regularly be found in the fecal excretions of paralyzed individuals, as well as of many other individuals who failed to exhibit any of the clinical signs of disease.[22-25]

Of renewed interest also were earlier findings of virus in the nasopharyngeal washings of the family associates of patients and of individuals in the preparalytic period, findings later confirmed by the repeated isolation of virus from oropharyngeal washings and swabs of patients and of contacts.[26-28] Finally, it became apparent that paralytic as well as subclinical infection could be produced by simple feeding of virus to cynomolgus monkeys[29-31] or to anthropoid apes[9, 10, 13] without involvement of the olfactory system.

Other clearly established facts nevertheless supported the general acceptance of the idea that the pathogenesis of poliomyelitis differed radically from those neurotropic virus diseases which are characterized by a demonstrable viremia and which are transmissible to the mammalian host via infected arthropods, such as mosquitoes and ticks. First, virus was so rarely isolated from the blood of paralytic cases and of fatal cases that even the few positive isolations were considered with some degree of suspicion by most workers. Second, the distribution of lesions in the brain was so restricted as to contrast strik-

ingly with the arthropod-borne encephalitides, in which the presence of lesions in all regions of the brain pointed to a widespread passage of virus across vascular walls into the nervous tissue.

These, and other facts, and the presence of virus in the alimentary tract before onset of symptoms [32, 33] led to the idea that virus probably penetrates from the alimentary tract along nerve fibers to the central nervous system (CNS).[20, 34, 35, 36] Although some experimental evidence suggested possible nerves which might be involved, the evidence from human cases has never been, and still is not, conclusive, except possibly for cases of bulbar poliomyelitis following tonsillectomy. In our own studies, no consistent pattern of lesion distribution in peripheral ganglia could be found in human cases or in chimpanzees paralyzed after simple virus feeding which could point to a neural route of transmission to the CNS from the alimentary tract. Despite these difficulties, we entertained the hypothesis that the fifth, seventh, ninth, and tenth cranial nerves were the most likely routes of virus spread to the CNS.[35] In addition to the absence of critical evidence for neural spread of virus to the CNS, moreover, some early experiments suggested the possibility that under certain special conditions virus might make its way to the central nervous system from the periphery via a non-neural pathway. German and Trask, for example, showed that poliomyelitis infection could result in animals inoculated into completely denervated extremities.[37]

Some of our own early experiments could also be interpreted in this light, since in rhesus monkeys inoculated in the lumbar spinal cord after complete thoracic cord transection with dural ligation and bilateral sympathetic trunk section, poliomyelitis infection resulted in the central nervous system above the transection after a prolonged incubation period in a few instances.[38] Although we postulated a circuitous neural route for the virus, via the lower intestinal tract and the vagus nerve, I must admit that we were struggling hard to keep the virus within the confines of the nervous system. It must be added, however, that the trauma associated with both of these experiments may have made possible a viremia and a passage through part of the blood brain barrier which ordinarily would not have been penetrable in the rhesus monkey.

When we now add to these findings in experimental animals the evidence of Horstmann and of ours, that viremia is regularly present in the incubation period after simple virus feeding in cynomolgus monkeys and in chimpanzees, and that virus has actually been isolated from the blood of an early abortive case, the conclusion is plain that viremia is a factor still to be reckoned with in the pathogenesis of this disease.

The perhaps more important question next arises as to whether the virus in the blood is merely there as a casual event or whether it may be related to the subsequent invasion of the central nervous system in the *natural infection* or after virus feeding. Several observations contribute suggestive information in this connection. Our recent experimental work has demonstrated, for example, that passive immunization, before challenge by simple virus feeding,[39] with as little as 0.1 ml. of human gamma globulin per kilogram can prevent paralysis in cynomolgus monkeys. The serum antibody level produced by the gamma globulin is at the borderline of detectability, whereas levels 500 times greater are insufficient to prevent the establishment of intestinal infection in chimpanzees as evidenced by fecal virus excretion.[8] Moreover, a prophylactic serum antibody level 100 times greater than that which completely protects cynomolgus monkeys challenged by simple feeding fails to prevent paralytic

TABLE 1

The Influence of Gamma Globulin on Prophylaxis and Therapy after Intranasal Inoculation in Rhesus Monkeys *

	Approximate Intranasal Virus Dose	*Poliomyelitis Rate* †	*Prostrating Paralysis*	*Fever*	*Incubation Period in Days*	*Onset of Paralysis, Days after Onset of Fever*
Experiment 1						
Controls	10	5/6	4/6	5/6	9–11	3, 3, 1, 3, NP ‡
Treated on first day of fever		5/6 **	5/6	5/6	8–10	4, 3, 2, 3, 5
Experiment 2						
Controls	10	5/6	5/6	6/6	7–9	3, 3, 3, 4, 2
Treated 1 hour before inoculation		3/6	0/6	6/6	10–12	4, 1, 5
Experiment 3						
Controls	3	6/6	3/6	6/6	8–11	3, 3, 3, 3, 5, 5
Treated 24 hours before inoculation		2/6	1/6	5/6	9–11	4, 6

* The gamma globulin was given intramuscularly in a dose of 10 ml. per kilogram in every instance. Brunhilde virus was used for inoculation on 2 successive days.

† Negative monkeys had no lesions in olfactory bulbs.

‡ NP = Nonparalytic poliomyelitis.

** Only 5 were treated.

poliomyelitis in rhesus monkeys inoculated by a known neural pathway, the olfactory route, when a not greatly larger virus dose is used. Table 1 shows that in rhesus monkeys inoculated intranasally with approximately 3 intranasal PD_{50} (Experiment 3), only a partial protective effect is shown, although 10 ml. of gamma globulin per kilogram were administered 24 hours before inoculation. No protective effect of gamma globulin appeared when the same amount of gamma globulin was administered at the first sign of fever following intranasal inoculation (Experiment 1). These experiments suggest that antibody in large amounts is not only ineffective in therapy at the first sign of infection following inoculation by a peripheral route which has a *known* neural pathway to the central nervous system, but is also relatively ineffective prophylactically under the same conditions.

Another line of evidence which supports the concept of spread of virus to the central nervous system from the blood after virus feeding is more direct. In a series of 23 cynomolgus monkeys fed Mahoney (Type 1) virus on 3 successive days, 12 were paralyzed and 11 remained well. Of those paralyzed, 6 were shown to have viremia on the seventh day after the first virus feeding, whereas none of the 11 which remained well had a demonstrable viremia on the same day (Table 2). Seven of the paralyzed monkeys which were bled on the day of onset of paralysis had no demonstrable viremia at that time. This experiment suggests a relationship between viremia in the incubation period and the subsequent development of paralysis, which, however, will require confirmatory evidence. Although the correlation between viremia and paralytic infection may be high when virulent strains, such as the Mahoney strain, are involved, a lesser degree of correlation may be found with strains of lower virulence. In Horstmann's series,[7] viremia occurred in two cynomolgus monkeys which had no apparent disease, although the absence of central nervous system invasions was apparently not confirmed by post-mortem histological

TABLE 2

Relation of Viremia to Paralysis in Cynomolgus Monkeys after Feeding Poliomyelitis Virus *

Paralyzed Monkeys	*Viremia on 7th Day after Initial Feeding*	*Viremia on Day of Paralysis*	*Incubation Period in Days from First Feeding*
K-549	+	— —	14
K-553	+	— —	14
K-547	+ +	— —	10
K-665	+		10
K-669	+		9
K-662	+		9
K-552	—	— —	13
K-546	— —	— —	10
K-550	— —	— —	10
K-663	—		10
K-668	—		9
K-557		— —	7
Total	6/12 †		
Monkeys not Paralyzed			
K-545	—		
K-548	—		
K-551	—		
K-554	—		
K-555	—		
K-556	—		
K-664	—		
K-666	—		
K-667	—		
K-670	—		
K-671	—		
Total	0/11 †		

* 1 cc. of Mahoney virus (Type 1), containing approximately 10,000 intracerebral PD_{50}, was fed on 3 successive days. This apparently large dose, however, can be seen to be the equivalent of only 1 PD_{50} by the method of inoculation used.

+ = 1 monkey paralyzed after intracerebral inoculation with serum.

— = 1 monkey remained normal after intracerebral inoculation with serum.

† $X^2 = 5$. $P = 0.02$.

examination. In a recent experiment of our own in chimpanzees, one animal was shown to have had a viremia on the tenth day after virus feeding, but no paralytic infection developed, and no CNS lesions were demonstrable after sacrifice two months later. Finally, in human paralytic cases, as I mentioned, the presence of serum antibody at the onset of paralysis suggests, as it does in our chimpanzee experiments, that a preceding viremia was associated with the occurrence of paralysis.

It is clear that only additional research directed at this important issue will make possible a decision regarding the importance of viremia in relation to CNS infection. In the meantime, it is necessary to keep an open mind concerning the possibility that virus may penetrate into the CNS from the blood stream, perhaps by way of a point of greater penetrability such as the area postrema in the medulla oblongata. Entrance of virus at a single point would be consistent with the pathological picture of restricted lesions in the brain, in contrast with the indiscriminate distribution of lesions in the arthropod-borne encephalitides. If such entrance were effected through the area postrema in the floor of the fourth ventricle, the greater intensity of lesions which has often been observed in this region and along the central gray of the brain stem in human infections, and in orally inoculated chimpanzees and cynomolgus monkeys, could equally well be explained either by such penetration or by entrance along cranial nerves subserving the alimentary tract, as we have previously postulated.

Figure 3 shows the relationships discussed in schematic form, as well as possible pathways of spread from one virus phase to another. It can be seen that we postulate a phase of virus multiplication which has been given little attention before and which may be referred to as the vascular phase. This includes the blood, and perhaps organs in close relation to the blood stream (lymph nodes, spleen, kidneys, and possibly others), and from which virus has been isolated as late as the onset of paralysis and even at autopsy. Our hypothesis is that the vascular phase may be initiated by penetration of virus from the alimentary phase into the blood stream, or into regional lymph nodes. One can only speculate at this time regarding the mechanisms responsible for the vascular virus phase. Either large amounts of virus must find a way to the blood stream from the alimentary mucosa, or possibly small amounts leak through, with infection and multiplication of

SCHEMA OF

SITES OF VIRUS MULTIPLICATION IN POLIOMYELITIS

(Natural Infection and Experimental Virus Feeding)

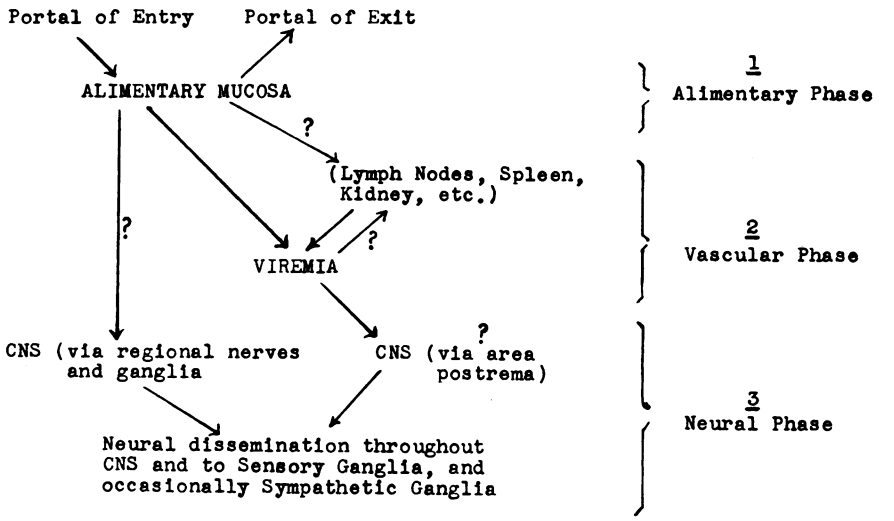

FIGURE 3—Schematic representation of sites of virus multiplication and possible pathways of dissemination in the body in the "natural" human infection, or after simple virus feeding in chimpanzee and cynomolgus monkeys.

virus resulting in the associated organs followed by excretion of virus in even larger amounts into the blood stream. Several facts tend to support the concept of an independent vascular phase of virus multiplication rather than the incidental occasional virus invasion of the blood suggested by others. First, the presence of a substantial concentration of virus in the blood of two chimpanzees [8] indicates more than mere leakage of virus from the alimentary phase in this species, but rather virus multiplication in a tissue in close association with the blood stream. Investigation of titers of virus in the preparalytic period in the walls of the small intestine or in lymph nodes and spleen may yield interesting information in this connection, since the source of the viremia should be an organ with at least as high a titer as that which may occur in the blood.

Unfortunately, the evidence from human cases is as yet fragmentary, and the study of this problem in human beings is seriously hampered by the probability that serum antibody is present when material is taken at autopsy. Sabin and Ward [40] isolated virus from a pool of lungs, liver, spleen, and kidneys of an autopsy case with the shortest duration of disease in their series (2.5 days). Separate assay of lung, liver, and kidney material was negative, so that there is a suggestion here that the spleen contained virus. Isolation of virus from a pool of axillary and inguinal lymph nodes from the same case has the same significance, but the isolation of virus from human axillary lymph nodes and mesenteric lymph nodes, in the absence of viremia, by Wenner and Paul is of considerable interest and importance.[41] The isolation

of virus by Sabin and Ward [42] from lymph nodes, spleen, kidney, and urinary bladder of cynomolgus monkeys paralyzed after virus feeding also is suggestive, but this finding must be qualified by the fact that the presence of virus in the blood was not excluded in the animals reported. Second, the ease of growing virus in tissue cultures of primate testes and kidney suggests that non-neural tissues, such as lymph nodes, spleen, or kidney may also be sources of virus proliferation in the intact host.

I now want to turn to the property of the virus which we call "neurotropism," namely, its ability to invade and to multiply in nervous tissue. This is a property which changes a harmless relationship of virus and human species into a disastrous event for those persons in whom the virus escapes from the alimentary tract and enters the nervous system. An understanding of the neurotropism of this virus, it is obvious, can do little to aid us in controlling the spread of poliomyelitis. It can help us, however, to understand the nature and the aftereffects of the disease, upon which palliative treatment and rehabilitation depend, and upon which may depend the effective use of chemotherapy —if a potent chemotherapeutic agent should ever be developed.

Within the central nervous system the ability of the poliomyelitis virus to traverse nerve fibers is expressed in a tendency to continue its spread along nerve fibers from one end of the central nervous system to the other. Unlike the neurotropic viruses which have generally been assumed to be disseminated by way of the blood stream—encephalitis viruses are an example—poliomyelitis viruses even in the severest infections reach only restricted regions of the brain and spinal cord. Several factors come into play here which have been clearly demonstrated by experimental work. First of all, the virus is fortunately unable to multiply in certain important parts of the brain, and it multiplies with some difficulty in other parts of the brain and spinal cord. This can be shown by inoculating virus directly into such areas in a susceptible animal like the monkey. Although virus will spread from such an area, for example, the visual area of the cerebral cortex, and will multiply in and destroy cells in adjacent areas, with resulting effects of inflammation, the resistant area will be unaffected.[43]

Another factor which limits the distribution of poliomyelitis in the central nervous system is an interesting one which is determined by the complicated topography of nerve fiber pathways in the nervous system. Because the virus appears to spread in the nervous system only by way of nerve fibers, it reaches only those centers which are connected directly, or indirectly, with the region into which it originally gained entry. For this reason, many regions of the brain which are capable of supporting the growth of the virus are rarely, if ever, reached by the virus and are spared its devastating effects.[43, 44] For example, most of the cerebral cortex is spared for this reason, because as a rule, the spread of virus from lower parts of the brain, where peripheral nerves enter, extends only to a relatively small part of the cerebral cortex which is known as the motor area. For this reason, it is one of the fortunate facts about poliomyelitis that intellectual functions are unaffected, in spite of severe paralysis and other symptoms, since the primary seat of these functions, the cerebral cortex, is largely spared. Of course, one might wonder why the virus does not spread from the motor area to involve the rest of the cerebral cortex with which it is connected. Apparently the reason for this is twofold. The cerebral cortex, including the motor cortex, is not very susceptible as compared with lower parts of the brain and spinal

cord, and, moreover, since the motor cortex is at the end of a series of nerve fiber pathways traversed by the virus, it is probably reached by a relatively low concentration of virus which is soon neutralized by defensive mechanisms which come into play as the disease progresses.

The centers of the brain which are most affected by the multiplication of the virus are the motor centers of the lower part of the brain—the brain stem —and the spinal cord. In the motor nerve cells, which control the movement of muscles by means of their elongated protoplasmic expansions, the motor nerve fibers, the unfortunate excursion of the poliomyelitis virus from the intestinal tract reaches a culmination of reproductive frenzy which, for a short time, produces the highest concentrations of poliomyelitis virus of which we know and as a result the destruction or temporary injury of the nerve cells in which the multiplication takes place.[45] Space does not permit a detailed discussion of the microscopical aspects of this drama, in which the virus multiplication results in destruction both of host cells and of virus. It is interesting that the rapid increase in virus concentration at the onset of the infection in the nervous tissue is followed in a day or two by an almost equally precipitous decline of virus concentration in animals which recover.[46] This precipitous fall of virus concentration cannot be explained by the destruction of all susceptible nerve cells, because in many mild infections there are numerous nerve cells still available which are apparently spared by other factors which are responsible for subsidence of the disease process.

It is these factors which I wish to discuss in my concluding remarks. For, as a biological entity, the virus cannot escape an important consequence of being one, namely, its antigenicity. As soon as multiplication of the small invading amount of virus begins, the antibody forming mechanism of the body comes into play. Unfortunately, in many instances, the mobilization of the body's immunity mechanisms is too slow to affect the outcome of rapidly fatal infections. It is probable that other more slowly progressing infections *are* favorably influenced by immunity processes occurring during the course of infection. If for no other reason, we can suspect this because of the rapidity of the decline of virus concentration in the spinal cord during the early recovery period. Moreover, we know that in a part of the alimentary tract where antibody from the blood has ready access, the throat, virus persists for only a few days in an infected individual; whereas in the lower alimentary tract, where it is apparently less readily reached by blood antibody, virus may persist for several weeks or longer in many instances.

The time-course and magnitude of specific serum antibody rise in the natural paralytic infection as well as in human beings experiencing silent infection following virus feeding, and in chimpanzees and cynomolgus monkeys infected by virus feeding, is fairly well known. The response in all appears to be essentially the same, so that we may suppose that evidence regarding the sources of serum antibody production from the experimental animal may be applied to our understanding of the process of immunogenesis in human beings. Indeed, if serum antibody production is a resultant of the three phases of virus proliferation hypothesized in this report, only indirect experimental evidence can reveal the role of each of these virus phases in serum antibody production.

First of all, it is clear from experimental work that the disease in the CNS after intracerebral inoculation results in only a poor serum antibody response [47, 48] which is, moreover, slower

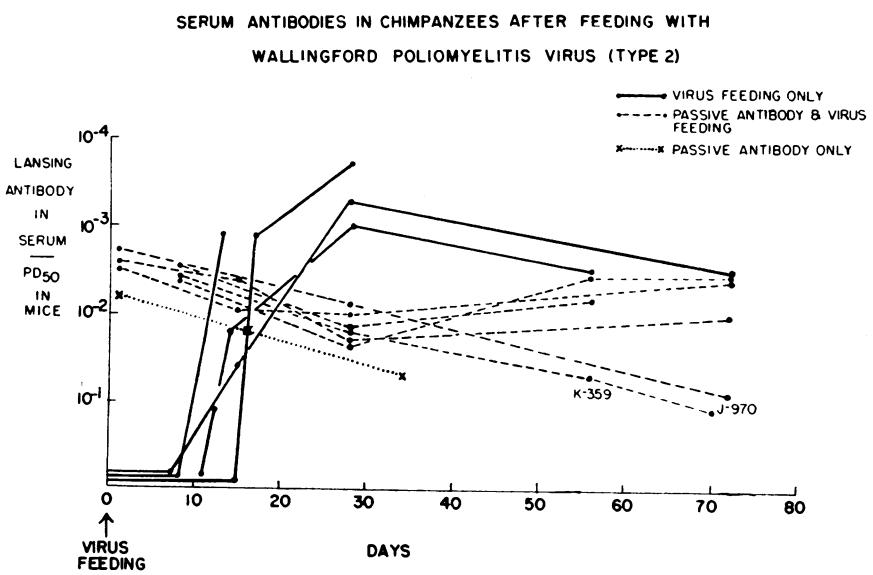

FIGURE 4—Summary of all chimpanzee experiments in which Lansing serum antibody was absent prior to onset of experiment. It can be observed that animals which were passively immunized at the time of virus feeding showed a passive decline of antibody during a period of at least 4 weeks, and that all but 2 (J-970, K-359) showed a subsequent active antibody response.

in reaching its peak than that following alimentary infection.[49] This suggests that the neural phase of virus multiplication contributes little to serum antibody production in human infections, in which the antibody levels observed in silent infections are as high and as rapid in being achieved as in paralytic infection.[11]

It is then apparently necessary only to dissociate the respective roles of the alimentary phase and the vascular phase of virus multiplication in producing serum antibody. It is clear that when both of these phases occur, as in the chimpanzees described in this report, a sharp and high serum antibody rise occurs in the acute phase of the paralytic disease, with the peak reached within a week or two after onset of paralysis. In order to assess the role of the alimentary virus phase in this response, we may study the nature of the response which occurs in similarly inoculated chimpanzees which have received sufficient passive antibody to eliminate viremia. Several chimpanzees, inoculated at the same time as those mentioned earlier in this report, may be examined with this point in mind. Each received on the day of virus feeding enough specific hyperimmune serum to produce a serum titer in the chimpanzee of about 1:500. In an animal which was given the same dose of passive antibody and was not fed virus, the declining passive antibody in time indicates the rate of decay of passive antibody, which corresponds to a straight line on a semi-logarithmic scale (Figure 4). This straight line relationship indicates that the antibody behaves as homologous antibody, with an estimated half-life of the order of 12 days, similar to that observed in human adults.[50] This curve of decline of passive antibody in the normal chimpanzee contrasts in an interesting way with the time-titer curves of the chimpanzees which were fed virus immediately after receiving passive antibody. These animals had no clinical signs or lesions in the CNS, but excreted fecal virus. They also showed an initial decline of passive antibody, but this was followed

TABLE 3

Summary of Chimpanzee Experiments Testing Effects of Passive Immunization with Hyperimmune Serum on Sequelae of Simple Virus Feeding

	Virus Used for Feeding	Clinical-Path. Findings			Virus in Feces—Weeks *			Viremia Titer	Serum Antibody Titer †			
		Fever	Day of Paralysis	Cord Lesions	1 2	3	4		Pre-Immunology	Post Immunology	1 Month	2 Months
Controls												
J-965	Wfd.	—	—	—	+	+	+	—	—	—	3.5	2.5
J-967	"	+	17	+	+	—	—	$10^{-0.5}$ (15) ‡	—	—	3.7	
J-969	"	+	13	+	+			$10^{-1.5}$ (8)			3.0	
K-487	"	—	—	+	+	—	—	$10^{-1.5}$ (8, 11)	—	—	2.7	2.5
Immunized—active antibody response												
J-966	Wfd.	—	—	—	—	+	—	—	—	2.3	1.7	2.0
J-968	"	—	—	—	—	+	+	—	—	2.4	2.0	2.4
K-358	"	—	—	—	+	—	+	—	—	2.3	2.0	2.0
K-361	"	—	—	—	+	+	+	—	—	2.5	1.8	2.2
Immunized—no active antibody response												
J-970	Wfd.	—	—	—	—	—	—	—	—	2.7	2.1	1.1
K-359	"	—	—	—	+	—	—	—	—	2.3	1.9	1.1

* Based on intranasal inoculation of two rhesus monkeys with each specimen. + = 1 or 2 monkeys paralyzed. — = neither of 2 monkeys paralyzed.

† Based on duplicate or triplicate mouse neutralization tests with 32 PD_{50} Lansing virus. Titers are expressed as negative logs of serum dilutions which protect 50 per cent of the mice. — = no demonstrable antibody.

‡ Figures in parentheses are days when virus was isolated from blood stream.

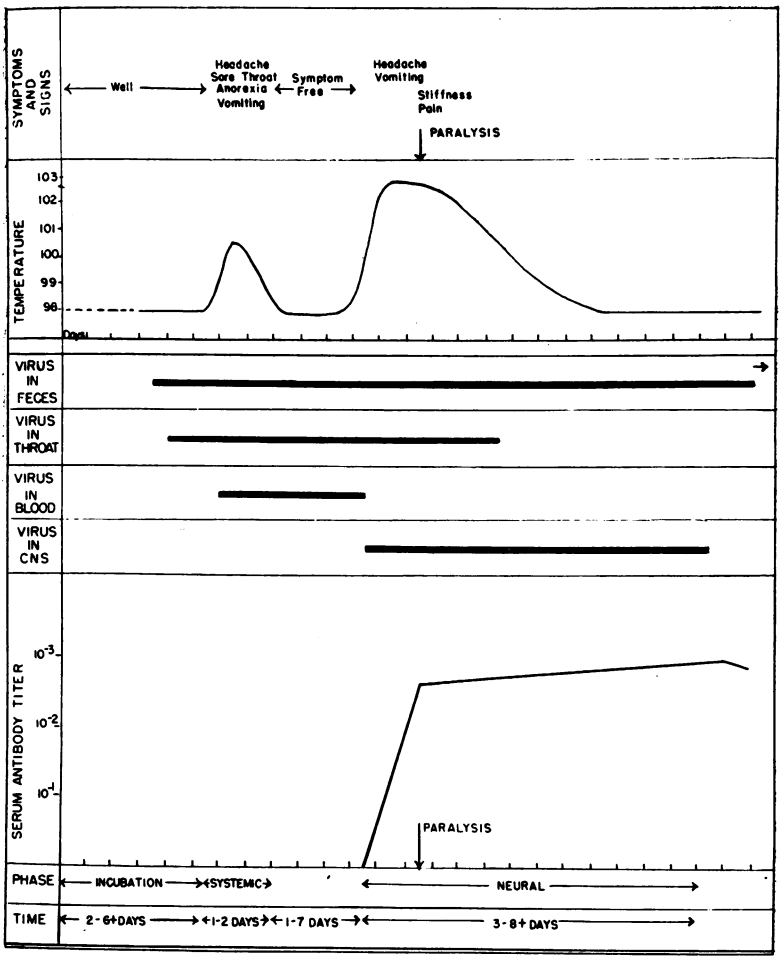

FIGURE 5—The time course of clinical, pathogenetic, and immunogenetic events occurring in "natural" paralytic infection, schematized in a partly speculative way.

by a delayed rise in titer after about one month. At 72 days their titers exceeded those which would be expected from passive decay alone by 10 to 30-fold respectively. Figure 4 and Table 3 show the antibody responses of these chimpanzees as compared with the chimpanzees which do not receive passive antibody.

Although there is a possibility that the delayed active antibody rise in these chimpanzees, as compared with the rapid antibody rise in the paralyzed animals, is correlated with a reduction of fecal virus excretion caused by the passive antibody, our evidence does not show such an effect. Another explanation of the result is that the delay in active antibody response was due to prevention of the vascular virus phase by the passive antibody. It would follow from this that it is the vascular phase which is responsible for the most rapid and highest serum antibody response, and also that the alimentary phase is capable of producing levels of serum antibody of 1:100, and over, in the absence of the vascular phase, but at a slower

rate than that which is observed in the cases which showed viremia.

A schematic correlation of clinical, pathogenetic, and immunogenetic phenomena which appear to be characteristic of the "natural" paralytic infection is shown in Figure 5, in which the time course and duration of clinical signs is adapted from Horstmann's description of the "childhood type" of clinical course.[51] The virus phases and antibody response as shown in this diagram represent a synthesis of information derived from the studies of human and experimental infections referred to in this lecture.

In conclusion, I should like to say a few words about the practical significance of the concepts just presented. If viremia is, in fact, a constant characteristic of the preparalytic period of poliomyelitis infection, or possibly a characteristic of infection with only certain "virulent" strains, a number of important consequences emerge. If it is postulated that virus may penetrate the CNS from the blood stream, it is clear that this penetration is only a rare occurrence among the much greater number of subclinical infections, so that the reason for this "accident" may be sought perhaps in unusual physiological or pathological circumstances. The possible effects of seasonal factors, of physical activity, of pregnancy, of trauma, or of concurrent infections with other agents on vascular permeability become the logical objects of suspicion and curiosity. It seems possible that the finding of Schwartzman, that cortisone increases susceptibility to poliomyelitic paralysis in ordinarily poorly susceptible species like the hamster,[52] will open the way to a rational interpretation of the role of some of the factors which appear to predispose to paralytic consequences of poliomyelitic infection. Whether the critical action of cortisone or related hormones is upon vascular penetrability, on virus multiplication in the CNS or in viscera, or on the inflammatory or immune responses remains to be determined. Possibly several modes of action of this versatile substance will be revealed by further research. Moreover, the mere existence of viremia, in any case, offers one reasonable explanation for the localization of virus at traumatic sites, such as those produced by inoculation procedures as pertussis vaccination,[53] with possible spread to injured nerve fibers and thence to the CNS along the regional nerve. This neural penetration from traumatic sites would be consistent with the frequently reported localization of paralysis in the limb affected by trauma.

The role of viremia in the pathogenesis of poliomyelitis is also of great importance in connection with immunological aspects of this disease. If viremia is, indeed, a necessary precursor of CNS infection, it is clear that low levels of serum antibody, whether derived from naturally or artificially acquired passive or active immunity, should theoretically be effective in preventing paralytic disease. I want to emphasize, however, that in the monkey experiments which I described, and in which very low levels of antibody were effective, the conditions were carefully controlled in regard to dose of antibody, time of administration, and time of exposure. These variables will have to be intensively investigated in human beings before we can deal effectively with the problem of immunoprophylaxis in human beings. Until then the indiscriminate use of scarce materials such as human gamma globulin will hamper rather than aid our attempts to find out whether immunoprophylaxis is possible or is practical. We *must* first find out how much is necessary in man, when to administer it, and who is to receive it, or else there will be a tragic waste of this potentially valuable material.

Finally, this discussion makes it clear that among the points of attack of pos-

sible chemoprophylactic agents the blood phase of virus activity must be given important consideration, along with the alimentary phase and CNS phase. For example, agents which act directly upon the virus, rather than on its substrate in host cells, might conceivably block viral entry into the CNS from the blood stream. It is evident that further research is needed to establish the frequency of occurrence of viremia in the incubation period of the human infection, and its possible role in the invasion of the CNS.

REFERENCES

1. Enders, J. F., Weller, T. H., and Robbins, F. C. Cultivation of the Lansing Strain of Poliomyelitis Virus in Cultures of Various Human Embryonic Tissues. *Science* 109:85, 1949.
2. Hammon, W. McD., and Roberts, E. C. Serum Neutralizing Antibodies to the Infecting Strain of Virus in Poliomyelitis Patients. *Proc. Soc. Exper. Biol. & Med.* 69:256, 1948.
3. Steigman, A. J., and Sabin, A. B. Antibody Response of Patients with Poliomyelitis to Virus Recovered from Their Own Alimentary Tract. *J. Exper. Med.* 90:349, 1949.
4. Bodian, D. Second Attacks of Paralytic Poliomyelitis in Human Beings in Relation to Immunity, Virus Types and Virulence. *Am. J. Hyg.* 54:174, 1951.
5. Ward, R., Horstmann, D. M., and Melnick, J. L. The Isolation of Poliomyelitis Virus from Human Extra-Neutral Sources. IV. Search for Virus in the Blood of Patients. *J. Clin. Investigation* 25:284, 1946.
6. Koprowski, H., Norton, T. W., and McDermott, W. Isolation of Poliomyelitis Virus from Human Serum by Direct Inoculation into a Laboratory Mouse. *Pub. Health Rep.* 62:1467, 1947.
7. Horstmann, D. M. Poliomyelitis Virus in Blood of Orally Infected Monkeys and Chimpanzees. *Proc. Soc. Exper. Biol. & Med.* 79:417, 1952.
8. Bodian, D. A Reconsideration of the Pathogenesis of Poliomyelitis. *Am. J. Hyg.* 55:414, 1952.
9. Howe, H. A., and Bodian, D. Poliomyelitis in the Chimpanzee: A Clinical-Pathological Study. *Bull. Johns Hopkins Hosp.* 69:149, 1941.
10. Howe, H. A., Bodian, D., and Morgan, I. M. Subclinical Poliomyelitis in the Chimpanzee and its Relation to Alimentary Reinfection. *Am. J. Hyg.* 51:85, 1950.
11. Koprowski, H., Jervis, G. A., and Norton, T. W. Immune Responses in Human Volunteers upon Oral Administration of a Rodent-Adapted Strain of Poliomyelitis Virus. *Am. J. Hyg.* 55:108, 1952.
12. Müller, W. Spontane Poliomyelitis beim Schimpansen. *Monatschr. f. Kinderh.* 63:134, 1935.
13. Horstmann, D. M., and Melnick, J. L. Poliomyelitis in Chimpanzees. Studies in Homologous and Heterologous Immunity Following Inapparent Infection. *J. Exper. Med.* 91:573, 1950.
14. Howe, H. A., and Bodian, D. Poliomyelitis by Accidental Contagion in the Chimpanzee. *J. Exper. Med.* 80:383, 1944.
15. Landon, J. F., and Smith, L. W. *Poliomyelitis.* New York: Macmillan, 1934.
16. Swan, C. The Anatomical Distribution and Character of the Lesions of Poliomyelitis, with Special Reference to the Type of Cell Affected and to Portal of Entry of the Virus. *Australian J. Exper. Biol. & M. Sc.* 17:345, 1939.
17. Robertson, E. G. An Examination of the Olfactory Bulbs in Fatal Cases of Poliomyelitis During the Victorian Epidemic of 1937–1938. *M. J. Australia* 1:156, 1940.
18. Sabin, A. B. The Olfactory Bulbs in Human Poliomyelitis. *Am. J. Dis. Child.* 60:1313, 1940.
19. Bodian, D., and Howe, H. A. An Experimental Study of the Role of Neurones in the Dissemination of Poliomyelitis Virus in the Nervous System. *Brain* 63:135, 1940.
20. Howe, H. A., and Bodian, D. Neuropathological Evidence on the Portal of Entry Problem in Human Poliomyelitis. *Bull. Johns Hopkins Hosp.* 69:183, 1941.
21. Kling, C., Wernstedt, W., and Pettersson, A. Recherches sur le Mode de Propagation de la Paralysie Infantile Epidemique. *Ztschr. f. Immunitätsforsch u. Exper. Therap.* 12:316, 1912.
22. Trask, J. D., Vignec, A. J., and Paul, J. R. Isolation of Poliomyelitic Virus from Human Stools. *Proc. Soc. Exper. Biol. & Med.* 38:147, 1938.
23. Kramer, S. D., Hoskwith, B., and Grossman, L. H. Detection of the Virus of Poliomyelitis in the Nose and Throat and Gastro-intestinal Tract of Human Beings and Monkeys. *J. Exper. Med.* 69: 49, 1939.
24. Vignec, A. J., Paul, J. R., and Trask, J. D. Poliomyelitic Virus from Feces in Non-paralytic Poliomyelitis. II. Infectivity by Various Routes. *Proc. Soc. Exper. Biol. & Med.* 41:246, 1939.
25. Lépine, P., Sédallian, P., and Sautter, V. Sur la Presence du Virus Poliomyélitique dans les Matières Fécales et sa Longue Durée d'Elimination Chez un Porteur Sain. *Bull. Acad. de méd. Paris* 122:141, 1939.
26. Vignec, A. J., Paul, J. R., and Trask, J. D. The Recovery of the Virus of Poliomyelitis from Extra-Neural Sources in Man, with a Survey of the Literature. *Yale J. Biol. & Med.* 11:15, 1938.
27. Howe, H. A., Bodian, D., and Wenner, H. A. Further Observations on the Presence of Poliomyelitis Virus in the Human Oropharynx. *Bull. Johns Hopkins Hosp.* 76:19, 1945.
28. Howe, H. A., and Bodian, D. Isolation of Poliomyelitis Virus from the Throats of Symptomless Children. *Am. J. Hyg.* 45:219, 1947.
29. Faber, H. K., Silverberg, R. J., and Dong, L. Poliomyelitis in Philippine Cynomolgus Monkeys after Simple Virus Feeding. *Am. J. Hyg.* 48:94, 1948.
30. Melnick, J. L., and von Magnus, H. Comparative Susceptibility of Cynomolgus and Other Monkey Species to Poliomyelitis Virus by the Intracerebral and Oral Routes. *Am. J. Hyg.* 48:107, 1948.
31. Howe, H. A., and Bodian, D. Poliomyelitis in the Cynomolgus Monkey Following Oral Inoculation. *Am. J. Hyg.* 48:99, 1948.
32. Pearson, H. E., and Brown, G. C. Recovery of Virus from Throats of Poliomyelitis Patients. *Proc. Soc. Exper. Biol. & Med.* 66:503, 1947.
33. Schabel, F. M., Jr., Smith, H. T., Fishbein, W. I., and Casey, A. E. Stool Virus Recovery in Subclinical Poliomyelitis During Incubation, Febrile, and Convalescent Periods. *J. Infect. Dis.* 86:214, 1950.
34. Sabin, A. B. Bela Schick Lecture. Studies on the Natural History of Poliomyelitis. *J. Mt. Sinai Hosp.* 11:185, 1944.
35. Bodian, D., and Howe, H. A. The Significance of Lesions in Peripheral Ganglia in Chimpanzee and in Human Poliomyelitis. *J. Exper. Med.* 85:231, 1947.
36. Burnet, F. M., and Jackson, A. V. Poliomyelitis. 4. The Spread of Poliomyelitis Virus in Cynomolgus Monkeys with Particular Reference to Infection by the Pharyngeal-intestinal Route. *Australian J. Exper. Biol. M .& Sc.* 18:361, 1940.

37. German, W. J., and Trask, J. D. Cutaneous Infectivity in Experimental Poliomyelitis Increased Susceptibility after Neurosurgical Procedures. *J. Exper. Med.* 68:125, 1938.
38. Howe, H. A., and Bodian, D. The Effect of Spinal Transection on the Spread of Poliomyelitis Virus in the Nervous System of the Rhesus Monkey. *Bull. Johns Hopkins Hosp.* 69:86, 1941.
39. Bodian, D. Experimental Studies on Passive Immunization Against Poliomyelitis. II. The Prophylactic Effect of Human Gamma Globulin on Paralytic Poliomyelitis in Cynomolgus Monkeys after Virus Feeding. *Am. J. Hyg.* 56:78, 1952.
40. Sabin, A. B., and Ward, R. The Natural History of Human Poliomyelitis. I. Distribution of Virus in Nervous and Non-nervous Tissues. *J. Exper. Med.* 73:771, 1941.
41. Wenner, H. A., and Paul, J. R. Fatal Infection with Poliomyelitis Virus in a Laboratory Technician. Isolation of Virus from Lymph Nodes. *Am. J. Med. Sc.* 213:9, 1947.
42. Quoted in Reference 34.
43. Bodian, D., and Howe, H. A. Neurotropism and the Genesis of Cerebral Lesions in Poliomyelitis: An Experimental Study. *Bull. Johns Hopkins Hosp.* 68:58, 1941.
44. Bodian, D., and Howe, H. A. Experimental Nonparalytic Poliomyelitis: Frequency and Range of Pathological Involvement. *Bull. Johns Hopkins Hosp.* 76:1, 1945.
45. Bodian, D. The Virus, the Nerve Cell, and Paralysis. A Study of Experimental Poliomyelitis in the Spinal Cord. *Bull. Johns Hopkins Hosp.* 83:1, 1948.
46. Bodian, D., and Cumberland, M. C. The Rise and Decline of Poliomyelitis Virus Levels in Infected Nervous Tissue. *Am. J. Hyg.* 45:226, 1947.
47. Sabin, A. B., and Olitsky, P. K. Humoral Antibodies and Resistance of Vaccinated and Convalescent Monkeys to Poliomyelitis Virus. *J. Exper. Med.* 64:739, 1936.
48. Morgan, I. M. The Role of Antibody in Experimental Poliomyelitis. III. Distribution of Antibody In and Out of the Central Nervous System in Paralyzed Monkeys. *Am. J. Hyg.* 45:390, 1947.
49. von Magnus, H., and Melnick, J. L. Antibody Response in Monkeys Following Oral Administration of Poliomyelitis Virus. *J. Immunol.* 60:583, 1948.
50. Dixon, F. J., Talmage, D., and Maurer, P. H. Half-life of Homologous Gamma Globulin (Antibody) Molecules in Man, Dog, Rabbit, Guinea Pig and Mouse. *Federation Proc.* 11:466, 1952.
51. Horstmann, D. M. Clinical Aspects of Acute Poliomyelitis. *Am. J. Med.* 6:592, 1949.
52. Shwartzman, G. Enhancing Effect of Cortisone upon Poliomyelitis Infection (strain MEF1) in Hamsters and Mice. *Proc. Soc. Exper. Biol. & Med.* 75:835, 1950.
53. Geffen, D. H. The Incidence of Paralysis Occurring in London Children within Four Weeks after Immunisation. *M. Officer* 83:137, 1950.

First Dental Board Examination

The first certifying examination was given by the American Board of Dental Public Health in St. Louis, Mo., on September 12–13, 1952, as a result of which nine dentists have been certified by the Board: Drs. John E. Chrietzberg, H. Shirley Dwyer, John T. Fulton, Norman F. Gerrie, Thomas L. Hagan, William P. Kroschel, Frank E. Law, George A. Nevitt, and Carl L. Sebelius.

A second certifying examination will be given by the American Board of Dental Public Health in September, 1953, in Cleveland, Ohio. Candidates for examination under the waiver clause of the Board's Eligibility Requirements for Examination and Certification must submit applications to the secretary not later than January 1, 1953.

Information and application forms may be obtained from the secretary, Dr. Philip E. Blackerby, Jr., at 250 Champion Street, Battle Creek, Mich.